REMARKS/ARGUMENTS

After entry of this paper, the pending claims are 1-7, 25, and 27-40. Applicants would like to note that the Examiner had indicated on page 2 of the Office Action that claims 1, 7, and 27-40 were pending, but inadvertently omitted the proper pendency of claims 2-6 and 25. Applicants have therefore included claims 2-6 and 25 in the listing of pending claims.

Claim 35 was rewritten in independent form; claim 38 was amended to correct a clerical error; and claim 39 was amended as suggested by the Examiner in an effort to place the application in condition for allowance. No new matter is added by these amendments.

**Claim Objections**

(i) *Claims 35, 36, and 40 are objected to for being dependent on a rejected base claim, but are otherwise in condition for allowance.*

Applicants respectfully request reconsideration and withdrawal of this objection for the following reason.

In an effort to place the application in condition for allowance, claim 35 was rewritten in independent form. Claims 36 and 40 depend on claim 35 and thereby include this amendment. As amended, claims 35, 36, and 40 are in condition for allowance.

Reconsideration of this objection is requested.

(ii) *Claim 38 is objected to for assertedly having no antecedent basis for the phrase "said selective estrogen receptor modulator" in the penultimate line.*

Applicants respectfully request reconsideration and withdrawal of this objection for the following reason.

Applicants respectfully disagree with the Examiner's assertion that the phrase "said selective estrogen receptor modulator" in the last line of the claim has antecedent basis. As support, Applicants point to the preamble of the claim whereby the phrase "a selective estrogen receptor modulator" is utilized. However, in an effort to correct a clerical error in section (a) of the claim, Applicants amended claim 38 by specifying that

the compounds of the invention are delivered with selective estrogen receptor modulators.

Reconsideration of this objection is requested.

(iii) *Claim 39 is objected to for having assertedly "cumbersome" language.*

Applicants respectfully request reconsideration and withdrawal of this objection for the following reason.

In an effort to place the application in condition for allowance, the claims were amended as suggested by the Examiner.

Reconsideration of this objection is requested.

**35 USC § 103 Rejection**

*Claims 1-7, 25, and 27-34 are rejected under 35 USC § 103(a) over International Patent Publication No. WO 00/66570 ('570), Applicants' acknowledgement on page 4, lines 3-5 of the specification in view of US Patent Application Publication No. 2002/0061875 (Gast et al.).*

Applicants respectfully request reconsideration and withdrawal of this objection for the following reasons.

Applicants' disagree with the Examiner's assertion that the subgenus of compounds disclosed in the '570 reference at pages 7-19 is sufficiently small and particularly disclosed so as to have rendered obvious the presently claimed compounds.

The compounds of formula II of the presently claimed invention require that there is a H-atom at the 1-position, a doubly bonded S at the 2-position, a cyanopyrrole at the 5-position, and that there are no other substituents on the second fused ring. These requirements thereby only permit the following compounds in the present invention:

(i) $R^{1'}$ is methyl, $R^{2'}$ is methyl, and $R^{3'}$ is $C_1$ to $C_4$ alkyl;

(ii) $R^{1'}$ is methyl, $R^{2'}$ is ethyl, and $R^{3'}$ is $C_1$ to $C_4$ alkyl;

(iii) $R^{1'}$ is methyl, $R^{2'}$ is $CF_3$, and $R^{3'}$ is $C_1$ to $C_4$ alkyl;

(iv) $R^{1'}$ is ethyl, $R^{2'}$ is ethyl, and $R^{3'}$ is $C_1$ to $C_4$ alkyl;

(v) $R^{1'}$ is ethyl, $R^{2'}$ is trifluoromethyl, and $R^{3'}$ is $C_1$ to $C_4$ alkyl;

(vi) $R^{1'}$ is $CF_3$, $R^{2'}$ is $CF_3$, and $R^{3'}$ is $C_1$ to $C_4$ alkyl; and

(vii) $R^{1'}$ and $R^{2'}$ are joined to form a spirocyclic ring containing 3 to 7 carbon atoms and $R^{3'}$ is $C_1$ to $C_4$ alkyl.

'570, however, permits a large variety of other substituents as noted on pages 7-10, which include:

(a) at least 10 substituents at the 1-position;

(b) at least 3 substituents at the 2-position;

(c) at least 15 substituents other than those noted above for $R^{1'}$ and $R^{2'}$ at the 3-position;

(d) at least 9 substituents that can be bound to the second ring; and

(e) countless numbers of rings that can be bound to the 5-position.

If one were to count the number of possibilities for (a)-(e), the final number of compounds covered by the same would be sufficiently larger than the small number of compounds encompassed by the pending claims.

Further, even the smallest generic structure on pages 14-15 of '570 has numerous possibilities of compounds including:

(a) at least 6 substituents at the 1-position;

(b) at least 3 substituents at the 2-position;

(c) 2 substituents at the 3-position;

(d) 3 substituents that can be found to the second ring; and

(e) 2 different ring systems:

a benzene ring containing 10 combinations of substituents; or

a 5-membered heterocyclic ring containing about 19 combinations of substituents.

Again, if one were to count the number of possibilities for (a)-(e), the final number of compounds covered by the same would be sufficiently larger than the small number of compounds encompassed by the pending claims. Therefore, Applicants' respectfully assert that this subgenus is not "sufficiently small" as stated by the Examiner and could not possibly make obvious the presently claimed invention. Nor does

Applicants' acknowledgement or Gast add anything to '570 to suggest Applicants' invention.

Therefore, '570 alone or in combination with Applicants' acknowledgement and Gast does not suggest Applicants' invention.

Applicants' disagree with the Examiner's assertion that direction is given in the '570 reference for using each and every one of the disclosed substituents in a manner such that the presently claimed compounds would have clearly been obvious to one of ordinary skill in the art.

Applicants respectfully disagree with the Examiner and note that '570 does not provide any suggestion or motivation to select the specific compounds of Applicants' invention whereby:

(a) a H-atom must be at the 1-position;

(b) a S-atom must be doubly bonded to the C-atom at the 2-position;

(c) methyl, ethyl, or $CF_3$ groups, or a spirocyclic ring must be at the 3-position;

(d) the second fused ring can only contain a cyanopyrrole ring of the noted structure; and

(e) the N-atom of the pyrrole ring must be substituted an alkyl.

In fact, there is no specific recitation or support in '570 that literally or inherently states or motivates one to select these specific substituents (a)-(e). Nor did the Examiner point to any express teaching in '570 (as required by MPEP 2144.08 (II)(b) and reiterated by the Examiner in the outstanding Office Action) that would lead one to select the claimed species or subgenus of Applicants' invention. There is absolutely no direction in '570 to select the presently claimed substituents "...in a manner such that the presently claimed compounds would have clearly been obvious to one of ordinary skill in the art". Instead, it is only Applicants that determined that this combination of substituents would be preferable and would be useful in the present invention. Nor does Applicants' acknowledgement or Gast add anything to '570 to suggest Applicants' invention.

Therefore, '570 alone or in combination with Applicants' acknowledgement and Gast does not suggest Applicants' invention.

The Examiner asserted that Applicants have not identified and explained the comparative data which would lead one to conclude that "the inventors found that the compounds exemplified by compounds of formula II have unexpected potency".

As requested by the Examiner, Applicants' point to the comparative data provided in the following documents which support Applicants' statement:

(i) Fensome et al., "Synthesis and Structure-Activity Relationship of Novel 6-Aryl-1,4-Dihydrobenzo[d][1,3]oxazine-2-thiones as Progesterone Receptor Modulators Leading to the Potent and Selective Nonsteroidal Progesterone Receptor Agonists Tanaproget", J. Med. Chem, 48:5092-5095 (2005);

(ii) Winneker, "Nonsteroidal Progesterone Receptor Modulators: Structure Activity Relationships", Bioorg. Med. Chem. Lett., 13:1313-1316 (2003); and

(iii) Zhang et al., "Novel 6-Aryl-1,4-Dihydrobenzo[d][1,3]oxazine-2-thiones as Potent, Selective, and Orally Active Nonsteroidal Progesterone Receptor Agonists", Bioorg. & Med. Chem. Lett., 13:1313-1316 (2003).

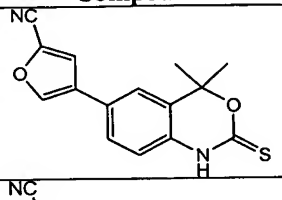
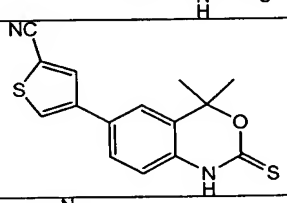
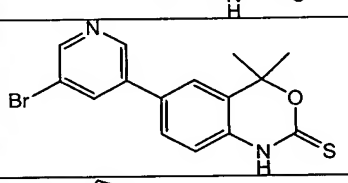
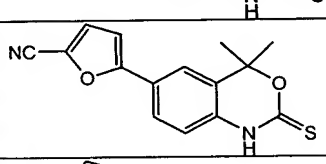
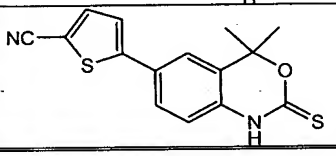
These documents are enclosed herewith in an Information Disclosure Statement for the Examiner's review and represent work performed by the assignee.

In these documents, data is provided that supports Applicants' assertion that the compounds of the presently claimed invention have superior agonistic activity over other cyclothiocarbamate compounds.

First, data for benzoxazin-2-thione compounds whereby the $R^5$ substituent (at the 6-position) is a heterocyclic group other than a pyrrole was provided in Fensome and Winneker and is reproduced below for the Examiner's convenience.

**Table 1**

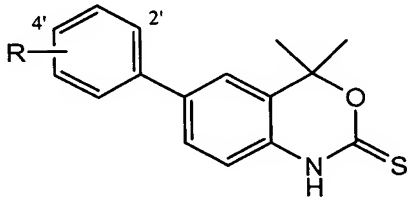
**$R^5$ is a Heterocyclic Group Other than a Pyrrole Ring**

| Compound | $EC_{50}$ (nM) |
|---|---|
|  | 1.2 [1] |
|  | 0.4 [1] |
|  | 5.7 [2] |
|  | 1.25 [3] |
|  | 0.7 [3] |

Second, data for benzoxazin-2-thione compounds whereby the $R^5$ substituent (at the 6-position) is substituted benzene ring was provided in Zhang and is reproduced below for the Examiner's convenience.

**Table 2**

**$R^5$ is a Substituted Benzene Ring**



[1] Data obtained from Fensome et al.

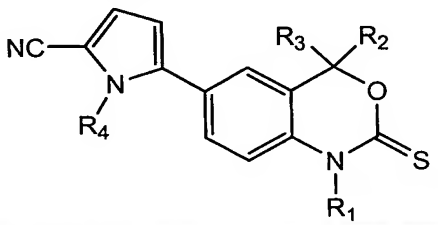
[2] Data obtained from Zhang et al.

| R | $EC_{50}$ (nM) | R | $EC_{50}$ (nM) |
|---|---|---|---|
| 2'-F | 11.6 | 3'-F, 5'-CN | 0.6 |
| 3'-F | 1.0 | 3'-F, 5'-OMe | 2.6 |
| 2'-Cl | 49.8 | 3'-F, 5'-$CF_3$ | 2.5 |
| 3'-Cl | 1.7 | 3'-Cl, 4'-F | 79.5 |
| 3'-Br | 2.5 | 3'-Cl, 5'-Cl | 26.5 |
| 3'-$NO_2$ | 1.1 | 3'-Cl, 5'-CN | 44.9 |
| 3'-CN | 0.4 | 3'-CN, 5'-CN | 42.0 |
| 3'-OMe | 7.2 | 3'-CN, 5'-Me | 200.0 |
| 2'-F, 3'-F | 1.5 | 3'-Br, 5'-CN | > 10000.0 |
| 3'-F, 4'-F | 11.4 | 3'-Br, 5'-Me | > 10000.0 |
| 3'-F, 5'-F | 1.5 | 3'-Br, 5'-$OCF_3$ | > 10000.0 |
| 3'-F, 5'-Cl | 0.9 | 3'-CN, 5'-$OCF_3$ | > 10000.0 |
| 3'-F, 5'-Br | 1.7 | 3'-CN, 5'-OMe | > 10000.0 |
| | | 3'-CN, 5'-OMe | > 10000.0 |

Finally, data for the presently claimed benzoxazin-2-thione compounds was provided in Fensome and is reproduced below for the Examiner's convenience.

**Table 3**

**Compounds of the Invention Whereby $R^5$ is a 2-Cyanopyrrole**




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $EC_{50}$ (nM) |
|---|---|---|---|---|
| H | Me | Me | H | 0.15 |
| H | Me | Me | Me | 0.15 |
| H | Et | Et | Me | 0.1 |
| H | -$(CH_2)_3$- | | Me | 0.5 |
| H | Me | Et | Me | 0.1 |
| H | Me | thien-2-yl | Me | 0.35 |

In summary and as the Examiner will note, the 2-cyanopyrrole benzoxazin-2-thione compounds clearly have better agonistic activity than the corresponding benzoxiazin-2-thione compounds having substituted benzene rings or heterocyclic rings, other than the 2-cyanoyrroles of the present invention, at the 6-position. Therefore, the combination of the H-atom at the 1-position, the alkyl or $CF_3$ groups at the 4-position,

and the designated 2-cyanoyrrole at the 6-position (whereby the N-atom of the pyrrole is alkylated) clearly results in PR agonists with superior properties.

To support Applicants' summary, Fensome provide the following comments:

(i) Page 5093, column 2: "[w]e further found that the nature of the substituent on the pyrrole (i.e., nitrile), its position on the pyrrole moiety, and the position of attachment of the pyrrole ring to the benzoazin-2-one nucleus were important features determining the functional activity. Only compounds with the 5'-cyano-2'-pyrrole motif resulted in PR agonist properties".

(ii) Page 5093, column 2: "...the combination of...the 5-cyanopyrrole and benzoxazin-2-thione, did yield a synergistic increase in potency. The unsubstituted **12** ($R_1$, $R_4$ = H, $R_2$, $R_3$ = Me) proved to be very potent in the T47D alkaline phosphatase assay ($EC_{50}$ = 0.15 nM). Alkylation of the pyrrole nitrogen leading to **13** ($R_4$ = Me) maintained this potency while methylation of the benzoxazin-2-thione led to **14**, which lost approximately 200-fold drop in potency ($EC_{50}$ = 21 nM).

(iii) Page 5093, column 2 - page 5094, column 1: "The small symmetrical substituents ($R_2$, $R_3$ = Me **15** and $R_2$ = Me, $R_3$ = Et **17**) typically maintained the same low nanomolar potency...[h]owever, the larger substituents, $R_2/R_3$ = spirocyclobutyl **16** and $R_2$ = Me, $R_3$ = 2-thienyl **18**, did lose between 3- and 50 fold in potency...".

Therefore, it is clear that the claimed compounds of formula II have unexpected potency over the general structure of compounds discussed in '570.

Therefore, no combination of '570 with Applicants' acknowledgement on page 4, lines 3-5 of the specification in view of Gast can suggest the presently claimed invention.

Reconsideration of this rejection is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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